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| 08/455,975      | 05/31/95    | RUBIN J              | 40399/299/NI        |

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EXAMINER

SAOUD, C

| ART UNIT | PAPER NUMBER |
|----------|--------------|
| 1646     | 23           |

DATE MAILED: 03/15/00

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

# Office Action Summary

Application No.  
08/455,975

Applicant(s)  
RUBIN et al.

Examiner  
Christine Saoud

Group Art Unit  
1646



☒ Responsive to communication(s) filed on Dec 28, 1999

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

## Disposition of Claims

☒ Claim(s) 38-121, 123-126, 128, 129, and 131-141 is/are pending in the application.

Of the above, claim(s) see para 5 of Office Action is/are withdrawn from consideration.

☒ Claim(s) 111-113 is/are allowed.

☒ Claim(s) 38-72, 82-110, 114-121, 123-126, 128, 129, and 131-141 is/are rejected.

☒ Claim(s) 73-81 is/are objected to.

☐ Claims \_\_\_\_\_ are subject to restriction or election requirement.

## Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on \_\_\_\_\_ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some\* ☐ None of the CERTIFIED copies of the priority documents have been  
☐ received.

☐ received in Application No. (Series Code/Serial Number) \_\_\_\_\_.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\*Certified copies not received: \_\_\_\_\_

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

## Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). \_\_\_\_\_

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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**DETAILED ACTION**

***Response to Amendment***

1. Claims 122, 127 and 130 have been canceled, claims 38, 49, 57, 63-64, 69, 82, 87-88, 90, 95, 110, 114, 121, 126, and 129 have been amended and claims 132-141 have been added as requested in the amendment of paper #22, filed 28 December 1999. Claims 38-121, 123-126, 128-129, and 131-141 are pending in the instant application.
2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
3. Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.
4. Applicant's arguments filed 28 December 1999 have been fully considered but they are not deemed to be persuasive.

Applicant requests confirmation that the amendment of 03 December 1998, paper #14, was entered. Confirmation was given in paper #15. The additional claims was the basis for the new restriction requirement of paper #15.

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***Election/Restriction***

5. Claims 38-121, 123-126, 128-129, and 131-141, in so far as they are directed to a method of inhibition by administration of heparin and a peptide, are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention. Election was made **without** traverse in Paper No. 19.

***Specification***

6. Applicant's substitute specification has been received and entered into the instant application. Any additional amendments that are deemed necessary by Applicant should be made in reference to the page and line numbering of the substitute specification. DO NOT send duplicate instructions for amendment referring to an original specification and a duplicate specification. Applicant should note that the duplicate instructions which were sent in paper #22 resulted in the clerical staff entering numerous amendments to the "original" specification. Due to our lack of staffing of the clerical areas, it would be prudent to avoid any unnecessary delays in processing amendments, etc. Your cooperation is greatly appreciated.

***Claim Rejections - 35 USC § 112***

7. Claims 38-56, 57-72, 82-101, 114-120, and 132-141 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for KGF and KGF polypeptides which have an amino acid sequence as set forth in Figure 7, or is truncated within the region of

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amino acids 32-78, does not reasonably provide enablement for any protein that (1) has a recited molecular weight, produced by fibroblast cells and has a specific activity as recited in the claims or (2) comprises a segment of the amino acid sequence of Figure 7, for the reasons of record in paper #20 as applied to claims 38-56, 57-72, 82-101, and 114-120. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicant argues that the amendment to claims 38, 49 and 114 to recite amino acids 32-78 of Figure 7 addresses the "concern about the essential features of the invention. This argument is not persuasive because this is the only structural element recited in the claims. As stated previously, the specification teaches a keratinocyte growth factor (KGF) of 194 amino acids in length and DNA encoding said KGF. The specification also teaches that the first 31 amino acids are a signal sequence that is cleaved in the mature protein and that amino acids 32-78 confer epithelial cell specificity to the protein. First, the language of a KGF polypeptide having a molecular weight and mitogenic activity does not give any structure to the amino acid sequence which is necessary for this activity. The claim must recite sufficient elements necessary for enablement of the claimed invention. The instant specification discloses a single protein that is isolated from fibroblast cells that has the recited activity of the claims and there is evidence in the specification that amino acids 32-78 are *responsible* for conferring cell specificity to the protein. There is no reasonable expectation that any other protein isolated from fibroblast cells that has a molecular weight as recited in the claims would have the claimed activity. Additionally, a

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molecular weight of between about 16 and 30 kDa plus amino acids 32-78 are still not sufficient to provide the mitogenic activity required by the claims. The claims do not recite sufficient elements necessary for the enablement of the claimed invention.

Claims 57 and 82 recite "comprising a sufficient number of amino acids 32-64 of Figure 7 to confer on said polypeptide mitogenic activity on BALB/MK keratinocyte cells", however, as pointed out before, there are no number of these amino acids which will provide for this activity. This is because these amino acids alone do not provide the biological activity of stimulating BALB/MK cells. These amino acids are responsible for conferring cell specificity.

8. Claims 49-56, 82-110, 121, 123-126, 128-129, 131, 134-135, and 138-139 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons of record in paper #20 as applied to claims 49-56, 82-110, and 121-131.

Applicant argues that KGF is a member of the FGF family, and that FGF is known to have wound healing activity. However, the specification fails to describe which amounts would be required to provide for the recited activity of the claims as outlined previously. Claims to a method of stimulating epithelial cell growth, in a patient, wherein the patient has a wound, wherein the patient has an epithelial cell condition, etc. would be enabled by the specification.

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However, when the claim requires a specific outcome, the claims must recite sufficient method steps to achieve this outcome. The specification fails to enable a method for treating a patient for any particular condition by stimulation or inhibition of KGF because there is no disclosure of such a method which would provide for the benefits of the instant claims. The claims must recite sufficient elements and steps for achieving the claimed method; without knowing what amount to administer and for what length of time, one of ordinary skill in the art would not be able to practice the invention as claimed. (See *In re Colianni* (CCPA) 195 USPQ 150.) The knowledge gained from the specification that KGF stimulates epithelial cells is not sufficient for a claim to accelerating or improving the healing of a wound because such a method is not provided for in the instant specification. Likewise, the fact that KGF can be inhibited *in vitro* does not provide for a method of treating a patient having an epithelial skin condition by inhibition of KGF. There is no evidence to support the conclusion that all epithelial skin conditions are caused by an over-expression of KGF, and therefore, could be treated by inhibition of KGF. There are no examples in the instant specification that inhibition of KGF will provide a therapeutic treatment for any known condition of the skin. Lastly, there is no specific method disclosed that would enable an artisan to practice the method as claimed. Therefore, the specification is not enabled for the claimed method, absent evidence to the contrary.

Applicant argues that "the law does not require one to exemplify every embodiment of the invention". Applicant is correct, and it would not appear that the rejection of record required such.

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Applicant argues, with regard to claims 110, 121, 123-126, 128 and the use of antibodies, that the rejection is a utility rejection. This is not persuasive because the rejection was made under 112 and how to use. If the rejection was a utility rejection, then the claims would have been rejected under 101. Applicant also argues that Alarid et al. and Sugimura use antibodies to KGF for inhibition of cell growth. However, Applicant should note that the methodology used by Alarid et al. and Sugimura is not found in the instant specification. Again, the specification does not provide any examples or strategies for a method of treating conditions that require specific inhibition of epithelial cells comprising administration of an antibody. There is insufficient information or nexus with respect to the ability of KGF antibodies (monoclonal, polyclonal, or neutralizing) to inhibit epithelial cells for treating conditions. The specification describes several types of antibodies (neutralizing, monoclonal, polyclonal, murine, rabbit), but the specification is deficient in teaching which, if any, of these antibodies is effective in specifically inhibiting epithelial cells. The claimed method encompasses the use of an antibody (any antibody) against KGF to specifically inhibit epithelial cells, however, other factors (especially aFGF) also stimulate epithelial cells (see Table I-1). It has not been established that the inhibition of a single growth factor would be effective for inhibiting epithelial cells and a person of ordinary skill in the art would not reasonable expect that the mere inhibition of KGF would result in inhibition of epithelial cells. With regard specifically to the enablement of the use of an antibody therapeutically, Harris et al. states that there is widespread acceptance that there is little future for the use of rodent monoclonal antibodies for *in vivo* human therapy (page 42, column 2) and that



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repeated dosing with chimeric antibodies is ineffective due to residual anti-idiotypic responses (page 42, column 3) (Tibtech, 1993). Humanized antibodies may still present serious problems with immunogenicity, since the idotype of such antibodies will contain unique amino acid sequences. Therefore, the rejection is maintained for the reasons provided above.

Applicant argues, with regard to claims 121-131 as directed to methods of inhibition by administration of a DNA probe, that page 58 of the specification provides probes that detect the antisense of an encoding sequence and that "[i]t is well known in the art that the antisense of DNA encoding sequence prevents transcription. Thus, the novel methods that encompass the use of DAN probes apply technology that is well known in the art" (see response at page 26). This argument is not persuasive because, whereas the use of a DNA probe to detect a specific DNA is old and well known in the art, use of a DNA probe in a therapeutic method is not old and well known in the art. The art of gene therapy and anti-sense therapy is very unpredictable at the present time, and even more so at the time of the instant invention. Without specifics of the method to be used (including probe length, composition, administration amounts, dosing schedules, etc.), the skilled artisan would not be able to practice the claimed method, absent evidence to the contrary. Such evidence has not been provided.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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10. Claims 133, 135, 137, 139, and 141 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The instant claims refer to a particular cellular response without a recitation of how that response is to be determined. Without knowing how the response is to be measured (i.e. different assays will provide for different results), the metes and bounds of the instant claims cannot be determined. The recitation of "as measured by percent of maximal H3-thymidine incorporation" would obviate this ground of rejection.

*Allowable Subject Matter*

11. Claims 73-81 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. If these claims were written in independent form directed to a method of stimulating epithelial cells comprising administering to a patient the polypeptides of these claims, these claims would appear to be allowable.

12. Claims 111-113 are allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after

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the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Saoud, Ph.D., whose telephone number is (703) 305-7519. The examiner can normally be reached on Monday to Friday from 8AM to 3PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623. The fax phone number for this Group is (703) 308-0294.

Official papers filed by fax should be directed to (703) 308-4227. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

March 13, 2000

**CHRISTINE SAOUD**  
**PATENT EXAMINER**

*Christine Saoud*